Editorial Comment

Role of NAD(P)H Oxidase and Its Regulation in Chronic Hypertension

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Oxidative stress is caused by the overproduction of oxidizing chemicals, which disrupts the balance between oxidizing power and reducing power. Oxidizing power is increased by the production of reactive oxygen species (ROS), including hydrogen peroxide, lipid peroxide, and radicals such as hydroxyl radical, hydroxyperoxyl radical, peroxyradical, nitric oxide, peroxynitrite and superoxide anion. Under physiological conditions, ROS act as a kind of scavenger to break down bacteria or unnecessary molecules. However, they can have undesirable effects when overproduced. Oxidative stress is considered to be involved in various pathological conditions, such as ischemic heart disease, vascular remodeling, nephropathy and brain damage (*1*–*3*).

Superoxide anion is one of the most important ROS involved in pathogenesis. Production of superoxide anion is facilitated by NAD(P)H oxidase, an enzyme composed of several membrane and intracellular components. The subunit proteins vary depending on the tissue. In the vascular wall, NAD(P)H oxidase consists of membrane components, such as gp91phox homologue (Nox1 and Nox4) and p22phox, and intracellular components, such as p47phox, rac1 and p67phox. When the cell is stimulated by one of various factors the intracellular components associate with membrane subunits and begin to produce superoxide anion from oxygen. The activity of NAD(P)H oxidase can be controlled by phosphorylation of subunits and/or association of subunits (*4*). Therefore, the activity of NAD(P)H oxidase is controlled, at least partly, by the expression of these subunits.

Recent studies indicate that oxidative stress also plays an important role in cardiovascular changes induced by hypertension. Chronic hypertension, including essential hypertension, is closely related to cardiovascular diseases, and the renin-angiotensin system plays a particularly important role in patients with chronic hypertension. Administrations of angiotensin converting enzyme (ACE) inhibitors or angiotensin II type 1 (AT_1) receptor blockers (ARBs) improve hypertension and hypertension-associated cardiovascular diseases. Many reports indicate that angiotensin II, a potent vasopressor, increases oxidative stress in the cardiovascular system through AT_1 receptor stimulation. Administration of angiotensin II has been shown to increase superoxide production, NAD(P)H oxidase activity, and pressor response (*5*, *6*). On the other hand, the increase in superoxide production, NAD(P)H oxidase activity and NAD(P)H oxidase subunit expression in experimental vascular injury were inhibited by ARBs without affecting blood pressure (*7*). These results suggest that angiotensin II modulates oxidative stress mainly by an increase in NAD(P)H oxidase activity through AT_1 receptor stimulation.

However, the role of angiotensin II in oxidative stress in chronic hypertension has not yet been totally clarified. As an animal model, stroke-prone spontaneously hypertensive rats (SHRSP) are widely used for studies on hypertension. It has been reported that SHRSP developed cardiac hypertrophy (*8*), brain abnormalities (*9*) and renal damage (*10*, *11*). In SHRSP, however, the changes in NAD(P)H oxidase subunits were not the same as those observed after continuous infusion of angiotensin II (*12*, *13*).

In an article appearing in this issue of *Hypertension Research*, Akasaki *et al*. (*14*) examined the involvement of NAD(P)H oxidase in vascular changes observed in chronic hypertension. The expression of the gp91phox homologues

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Nox1 and Nox4 in NAD(P)H oxidase subunits was increased in SHRSP in association with medial thickening and fibrosis of the aorta. In SHRSP, activation of the renin-angiotensin system is involved in continuous hypertension. An ARB, candesartan, suppresed the expression of Nox1 and Nox4 together with blood pressure in a dose-dependent manner. The treatment of animals with hydralazine plus hydrochlorothiazide also reduced both blood pressure and the expression of NAD(P)H oxidase subunits to levels similar to those achieved by an effective dose of candesartan. These observations indicate that chronic hypertension can up-regulate the expression of NAD(P)H oxidase subunits independent of the stimulation of AT_1 receptors, although the renin-angiotensin system is important in hypertension.

A close relationship between cardiovascular disease and metabolic disorders has been observed in patients with so-called metabolic syndrome. The importance of oxidative stress has also been reported in relation to metabolic changes. Recent studies suggest that oxidative stress may be involved in the development of glucose intolerance in insulin-sensitive organs, such as skeletal muscles (*15*). Angiotensin II seems to be at least partly involved in the insulin-resistance through oxidative stress (*15*). The relationship among hypertension, cardiovascular injury and metabolic disorders with respect to oxidative stress and the renin-angiotensin system is thus of great interest, and analyses of this relationship will become increasingly important in future studies.

References

1. Meerarani P, Badimon JJ, Zias E, Fuster V, Moreno PR: Metabolic syndrome and diabetic atherothrombosis: implications in vascular complications. *Curr Mol Med* 2006; **6**: 501–514.
2. Tagami M, Yamagata K, Ikeda K, *et al*: Genetic vulnerability of cortical neurons isolated from stroke-prone spontaneously hypertensive rats in hypoxia and oxygen reperfusion. *Hypertens Res* 1999; **22**: 23–29.
3. Yoshii T, Iwai M, Li Z, *et al*: Regression of atherosclerosis by amlodipine *via* anti-inflammatory and anti-oxidative stress actions. *Hypertens Res* 2006; **29**: 457–466.
4. Cheng ZJ, Vapaatalo H, Mervaala E: Angiotensin II and vascular inflammation. *Med Sci Monit* 2005; **11**: RA194–RA205.
5. Johar S, Cave AC, Narayanapanicker A, Grieve DJ, Shah AM: Aldosterone mediates angiotensin II–induced interstitial cardiac fibrosis *via* a Nox2-containing NADPH oxidase. *FASEB J* 2006; **20**: 1546–1548.
6. Zhao W, Swanson SA, Ye J, *et al*: Reactive oxygen species impair sympathetic vasoregulation in skeletal muscle in angiotensin II–dependent hypertension. *Hypertension* 2006; **48**: 637–643.
7. Iwai M, Chen R, Li Z, *et al*: Deletion of angiotensin II type 2 receptor exaggerated atherosclerosis in apolipoprotein E–null mice. *Circulation* 2005; **112**: 1636–1643.
8. Inomata H, Watanabe T, Iizuka Y, *et al*: Identification of quantitative trait loci for cardiac hypertrophy in two different strains of the spontaneously hypertensive rat. *Hypertens Res* 2005; **28**: 273–281.
9. Tagami M, Yamagata K, Ikeda K, *et al*: Genetic vulnerability of cortical neurons isolated from stroke-prone spontaneously hypertensive rats in hypoxia and oxygen reperfusion. *Hypertens Res* 1999; **22**: 23–29.
10. Goto M, Mukoyama M, Sugawara A, *et al*: Expression and role of angiotensin II type 2 receptor in the kidney and mesangial cells of spontaneously hypertensive rats. *Hypertens Res* 2002; **25**: 125–133.
11. Nakaya H, Sasamura H, Kitamura Y, *et al*: Effects of angiotensin inhibitors on renal injury and angiotensin receptor expression in early hypertensive nephrosclerosis. *Hypertens Res* 1999; **22**: 303–312.
12. Mollnau H, Wendt M, Szocs K, *et al*: Effects of angiotensin II infusion on the expression and function of NAD(P)H oxidase and components of nitric oxide/cGMP signaling. *Circ Res* 2002; **90**: E58–E65.
13. Zalba G, Beaumont FJ, San Jose G, *et al*: Vascular NADH/NADPH oxidase is involved in enhanced superoxide production in spontaneously hypertensive rats. *Hypertension* 2000; **35**: 1055–1061.
14. Akasaki T, Ohya Y, Kuroda J, *et al*: Increased expression of gp91phox homologues of NAD(P)H oxidase in the aortic media during chronic hypertension: involvement of the renin-angiotensin system. *Hypertens Res* 2006; **29**: 813–820
15. Shiuchi T, Iwai M, Li HS, *et al*: Angiotensin II type-1 receptor blocker valsartan enhances insulin sensitivity in skeletal muscles of diabetic mice. *Hypertension* 2004; **43**: 1003–1010.